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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/733,266	12/08/2000	Richard Kuo	STAN-209	3109

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EXAMINER
AFREMOVA, VERA

ART UNIT	PAPER NUMBER
1651	22

DATE MAILED: 04/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/733,266	Applicant(s) Kuo et al.
	Examiner Vera Afremova	Art Unit 1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 13, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-5, 13, and 15* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-5, 13, and 15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1, 3-5, 13 and 15 as amended [Paper No. 21 filed 1/13/2003] are pending and under examination in the instant office action.

Claims 2, 6-12, 14 and 16-18 were canceled by applicants.

Response to Arguments

Applicants' arguments filed 1/13/2003 have been fully considered but they are not persuasive for the reason below.

Claim Rejections - 35 USC § 112

New matter

Claims 1, 3, 4 and 15 as amended remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention as explained in the prior office action and for the reasons below.

Insertion of the limitation drawn to activated oocyte wherein the "oocyte has undergone at least one cell division" in claims 1 and 15 has no support in the as-filed specification. The insertion of this limitation is a new concept because it neither has literal support in the as-filed specification by way of generic disclosure, nor are there specific examples of the newly limited genus which would show possession of the concept of maintaining activated oocyte till the "oocyte has undergone at least one cell division" wherein the oocyte that has undergone at least

one cell division is an indication of oocyte activation after contacting with the claimed compounds.

The generic applicants' definitions of oocyte activation are drawn to calcium oscillation as well as to migration of pronuclei within the cell (specification page 5, lines 28-31) but not to cell division(s) as encompassed by the presently claimed method. There is some exemplified disclosure which demonstrates that calcium oscillation is an indication of activation of oocytes, for example: see Figure 4 or page 18, par. 2, wherein no cell division is disclosed as result of contacting cells with the claimed compounds. Thus, the disclosure of the specification as-filed is not a sufficient support for the new concept related to the indication of oocyte activation as presently claimed.

Applicants argue (response page 3) that one of skill in the art would understand that entry of a cell into mitotic cycle involves a commitment of the cell to undergo cell divisions, and, thus, one of skill in the art would recognize that the phrase "reentry into mitotic cell cycle" (specification page 5, line 29) supports the phrase "at least one cell division" as amended. However, the instant rejection is a matter of written description, not a question of what one of skill in the art would or would not have known. The material within the four corners of the as-filed specification must lead to the generic concept. If it does not, the material is new matter. Declarations and new references cannot demonstrate the possession of a concept after the fact. Thus, the insertion of the phrase "oocyte has undergone at least one cell division" is considered to be the insertion of new matter for the above reasons.

Indefinite

Claims 1, 3-5, 13 and 15 as amended remain/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention as explained in the prior office action and for the reasons below.

Claims 1, 5 and 15 as amended remain/are indefinite as related to the concept of oocyte activation. It is uncertain as presently amended what is measured in order to establish that oocytes are "non-activated" to provide cellular materials for the contacting step. It is also uncertain whether there are any differences in definitions of "oocyte activation" when related to "oocyte" in the absence of sperm (claim 1) and when related to "inseminated oocyte" (claim 15). Does oocyte of claim 1 undergo cell divisions in the absence of sperm or without fertilization with sperm?

Claim 15 as amended is unclear what oocyte (inseminated or non-inseminated) are activated. The phrase "said" (claim 15, line 4) does not point out what oocyte (non-activated or activated) are contacted with sperm.

Claim Rejections - 35 U.S.C. § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The insertion of new matter had resulted in the removal of the art rejection over the claims 1 and 15 under 35 U.S.C. 102(b) as being anticipated by Grumetto et al. [U] or over the

claims 1, 3, 5 and 15 under 35 U.S.C. 102(b) as being anticipated by Jawerbaum et al. [V] as explained in the prior office action. However, removal of new matter will result in the reinstatement of the art rejection(s).

Claims 1, 3, 4 and 15 as amended remain rejected under 35 U.S.C. 102(e) as being anticipated by US 6,255,109 [A] as explained in the prior office action and for the reasons below.

Claims are directed to a method of activating oocytes wherein the method comprises a step of contacting a "non-activated" oocyte with a donor of nitric oxide (NO donor) and step of maintaining until at least one cell division what indicates that the oocyte is activated. Some claims are drawn to activation in the absence of sperm in the method of activating oocytes. Some claims are drawn to activation for fertilization in the presence of sperm in the method of activating oocytes. Some claims are further drawn to the use of mammalian oocytes including human oocytes.

The cited US 6,255,109 [A] is relied as explained in the prior office action and repeated herein.

US 6,255,109 [A] discloses a method of promoting development of mammalian oocytes or activating oocytes wherein the method comprises step of contacting a "non-activated" oocyte with NO donor or sodium nitroprusside (SNP) and step of maintaining until the oocyte has undergone at least one cell division or more than one cell divisions (see table 1, col. 6). The cited patent discloses treatment of mammalian oocytes including bovine and human oocytes (col. 5,

line 12; col. 18, line 39). The oocytes were inseminated and, thus, the disclosed method comprises step of contacting oocyte with sperm as required by some of the claims (claim 15). The oocytes were treated with SNP after insemination and, thus, the maintaining step which "indicates" activation is performed in the absence of sperm suspension or in the absence of sperm as required by some of the claims (claim 1). The oocytes treated with SNP are maintained till they have undergone several cell divisions (table 1) and, thus, the maintaining step of the cited method indicates that the oocytes are activated as required by the presently claimed method. Thus, the cited patent appears to anticipate the claimed invention.

Applicants' argue that "oocyte" that is "inseminated" is not oocyte but embryo, thus, the method of cited patent is drawn to activation of "inseminated oocyte" or "embryo" (response page 6). Yet, the presently claimed invention is drawn to the use of "inseminated oocyte" for evaluation of oocyte activation (claim 15) and, thus, the cited method is drawn to "oocyte" activation within the meaning of the present claims. With respect to the claim 1 which requires oocyte activation in the absence of sperm, it is noted that "activation" is also evaluated by cell divisions as claimed and as argued. However, the claimed method does not exclude insemination step by the virtue of the open language "comprising", thus, whether or not sperm has been present during contacting step, the activation is evaluated by cell division which occurs after fertilization with sperm. Thus, the cited method is drawn to oocyte activation within the meaning of the claims as argued with respect to definitions of "oocyte activation".

Claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Herrero et al. [W] as explained in the prior office action and for the reasons below.

Claim is directed to a method of inhibiting oocyte activation during fertilization *in vitro* wherein the method comprises a step of contacting an oocyte with sperm and nitric oxide synthase inhibitor.

The cited reference by Herrero et al. [W] is relied as explained in the prior office action and repeated herein.

Herrero et al. [W] disclose a method of inhibiting oocyte activation during fertilization *in vitro* wherein the method comprises step of contacting mouse oocyte with sperm and various nitric oxide synthase inhibitors. The reference teaches the decrease of fertilization after the use of nitric oxide synthase inhibitors *in vitro* (table 1) and, thus, the cited reference teaches inhibition of oocyte activation during fertilization *in vitro* to the extend of the claimed invention.

Applicants argue that the method of Herrero is focused on contacting sperm with nitric oxide synthase inhibitor rather than contacting oocytes with nitric oxide synthase inhibitor (response page 7). Yet, the sequence of particular events, purity of cellular preparations and duration of steps are not limited by the claimed method. Thus, the cited method wherein oocytes are contacted with a sperm suspension which is a mixture of sperm and nitric oxide synthase inhibitor are considered to anticipate the present invention as claimed.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 3-5, 13 and 15 as amended remain rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,255,109 [A] and Herrero et al. [W] as explained in the prior office action and for the reasons below.

Claims are directed to a method of modulating activation of oocytes comprising steps of contacting an oocyte with a modulator of nitric oxide level such as a donor of NO or an inhibitor of nitric oxide synthase (NOS inhibitor) in the *in vitro* system and maintaining oocytes till at least one cell division. Some claims are further drawn to oocyte activation/modulation in the absence of sperm or prior to sperm addition. Some claims are further drawn to the use of oocytes including mammalian or human oocytes.

The cited references are relied as explained in the prior office action and repeated herein.

US 6,255,109 [A] and Herrero et al. [W] are relied for the disclosure of methods of modulating activation of "oocytes" with NO donors {US 6,255,109 [A]) and/or inhibitors of nitric oxide synthase {Herrero et al. [W]} and maintaining "oocytes" till cell divisions after treatment with NO level modulators. The cited references teach the use of various mammalian oocytes including mouse {Herrero et al. [W]}, bovine and humans {US 6,255,109 [A]}.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the present invention as claimed with a reasonable

expectation of success in activating oocytes intended for cell development and growth by treating oocytes with NO level modulators because it is known to use NO level modulators in the systems intended for oocyte development and growth. Thus, one of skill in the art would have been motivated to use compounds which are NO level modulators for the benefit of oocyte development and growth. The method of the present invention is related to activation of oocytes derived from a wide variety of animal species including invertebrate species, mammalians and etc. (specification page 9, line 11) as it is demonstrated by the cited prior art [U, V, IDS-AB]. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

Applicants argue that the cited references describe contacting "inseminated" or activated oocyte with the claimed compounds and, thus, they do teach methods similar to the presently claimed method (response page 8). In response to applicant's argument that the cited art is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the teaching of the cited references is clearly directed to effects of nitric oxide and/or inhibitor of nitric oxide synthase on survival and development of cells such as oocytes and/or embryos *in*

vitro, and, thus, the cited references are pertinent to the particular problem with which the applicants were concerned. Moreover, the definitions of "non-activated" oocyte are not provided by the as-filed specification. Further, when the "oocyte activation" is evaluated by cell divisions as claimed there is no differences in activation between the claimed cells such as "oocytes" and/or "inseminated oocytes" and the disclosed cells such as "embryos" in the methods for activating cells.

Claims 1, 3-5, 13 and 15 as amended remain rejected under 35 U.S.C. 103(a) as being unpatentable over Grumetto et al. [U] taken with Jawerbaum et al. [V] and US 6,077, 710 [IDS-AB] as explained in the prior office action and for the reasons below.

Claims are directed to a method of modulating activation of oocytes comprising step of contacting an oocyte with a modulator of nitric oxide level such as a donor of NO or an inhibitor of nitric oxide synthase (NOS inhibitor) in an *in vitro* system. Some claims are further drawn to oocyte activation/modulation in the absence of sperm or prior to sperm addition. Some claims are further drawn to the use of oocytes including mammalian or human oocytes.

The references by Grumetto et al. [U] and Jawerbaum et al. [V] are relied upon for the disclosure of methods of modulating activation of oocytes by contacting oocytes with modulators of NO levels such as NO donors or NOS inhibitors prior to sperm addition, insemination and, thus, prior to cell division(s).

For example, Jawerbaum et al. [V] disclose a method of modulating activation of mammalian oocytes comprising step of contacting *in vitro* cultured and maturated rat oocytes (page 392, par. 3, line 2) with modulators of nitric oxide levels such as NO donors (sodium nitroprusside, for example) and/or inhibitors of nitric oxide synthase (L-NAME, for example) in the absence of sperm. In particular, the cited reference teaches modulation of synthesis and accumulation of hormones which are involved in oocyte maturation, ovulation and fertilization processes.

The reference by Grumetto et al. [U] disclose a method of modulating activation of oocytes of the ascidian *Ciona intestnalis* wherein the method comprises a step of contacting an oocyte with a modulator of nitric oxide level or NO donor such as sodium nitroprusside in the *in vitro* system (abstract). The reference also discloses modulation of NO level or oocyte activation during fertilization (Fig. 4) in the presence of sperm. Further, the cited reference by Grumetto et al. [U] teaches an induction of fertilization current or Ca^{2+} currents by modulation of NO level (abstract). But the cited reference by Grumetto et al. [U] is lacking the teaching related to activation of mammalian oocytes.

However, the cited patent US 6,077, 710 [IDS-AB] teaches that activation of mammalian oocytes is a function of calcium (Ca^{2+}) (col. 2, line 42) and that parthenogenic activation of oocytes prior to nuclear transfer and related to repetitive transient elevations in intracellular Ca^{2+} in mammalian oocytes (col. 2, lines 47-50 and col. 3, lines 3-310) including various mammalian oocytes such as rabbit, bovine and/or mouse oocytes.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the present invention as claimed with a reasonable expectation of success in activating oocytes or inducing Ca^{2+} fluctuations in oocytes by treating oocytes with NO level modulators because the prior art teaches that activation of oocytes and/or fertilization channels are modulated by NO levels {Grumetto et al. [U]} and that activation of oocytes is related to Ca^{2+} fluctuations in oocytes including mammalian oocytes belonging to various mammalian species {US 6,077, 710 [IDS-AB]}. One of skill in the art would have been motivated to use compounds which are NO level modulators for the benefit of modulating Ca^{2+} fluctuations in the oocytes intended for future fertilization or nuclear transfers. The method of the present invention is related to activation of oocytes derived from a wide variety of animal species including invertebrate species, mammalians and etc. (specification page 9, line 11) as it is demonstrated by the cited prior art [U, V, IDS-AB]. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

With regard to the claims rejection under 35 U.S.C. § 103 applicants' main argument is directed to the idea that the references by Grumetto et al. [U] and by Jawerbaum et al. [V] fail to teach claim limitations such as cell division(s) after activation of oocytes with NO level modulators (see response page 9). However, according to the applicants' definitions and

examples in the as-filed specification, the oocyte activation is an increase (or fluctuation) of intracellular Ca^{2+} levels (see instant specification page 5, line 30-31 for definitions and Figures 4-6 for particular results) rather than cell division(s). No cell division is demonstrated by applicants as the result of oocyte treatment with modulators of NO level. The cited reference by Grumetto et al. [U] clearly teaches an increase of intracellular Ca^{2+} as the result of addition of NO donor to oocytes (see page 724, col. 2, par. 4, line 2-4). Therefore, the cited references are considered to be within the same field of endeavor and seek to solve the same problems as the instant applications and claims, and one of skill in the art is free to select components available in the prior art. In re Winslow, 151 USPQ 48 (CCPA, 1966).

Applicants also argued that the cited references combined do not provide any reasonable expectation of success or a clear connection between modulating NO levels and mammalian oocyte activation and/or fluctuations of Ca^{2+} levels (response page 10). This is not found particularly convincing since the references by Grumetto et al. [U] teaches an induction of fertilization current or fluctuations of Ca^{2+} levels by modulation of NO level (see abstract, for example). And the cited US 6,077, 710 [IDS-AB] teaches that activation of oocytes or reentry into mitotic cycle of mammalian oocytes is directly related to cellular activity which is a function of Ca^{2+} levels (col. 2, lines 32-42). 42) and that activation of oocytes of various mammalian species is characterized by fluctuations of intracellular Ca^{2+} levels (col. 3, lines 3-30).

Applicants also argue that *prima facie* case can not be established, if the references teach away (response page 10, last par.). However, the instant rejection is based on claim interpretation

in the light of applicants' specification definitions and disclosure. Thus, the cited references can not be said as teaching either away from the applicants' invention or being a non-analogous prior art.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova,

Art Unit 1651

April 2, 2003.

SANDRA E. SAUCIER
PRIMARY EXAMINER